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Epidemiological Study of Molecular and Genetic Classification in Adult Diffuse Glioma

Farajirad M[1]*, Farajirad E[2], Mahmoudi A[1] and Torabi S[1]

1Department of Neurosurgery, Mashhad University of Medical Sciences, Iran
[2]Resident Physician in Adult Neurology University of Toronto, Canada

***Corresponding author:** Mohammad Faraji-Rad, Professor of Neurosurgery, Department of Neurosurgery, Mashhad University of Medical Sciences, Mashhad, Iran, Email: farajirad@yahoo.com

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Abstract

Background: Mutations in isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) are frequent in low-grade and high-grade gliomas. However, the diagnostic criteria, in particular for gliomas, are highly various. The aim of our study was to establish genetic profiles for mutation and calcification of diffuse gliomas and to evaluate their predictive factors.
Methods: We estimate the different clinical and molecular characterization between IDH1, IDH2 mutant gliomas, p53, ATRX and 1p19q. In addition, whole-transcriptome sequencing and DNA extraction data were used to evaluate the distribution of genetic changes in IDH1 and IDH2 mutant gliomas in a Iranian high grade glioma.
Results: Between 2016-2019, among 53 gliomas in our study, 29 cases (54.7% %) harbored an IDH1,2 mutation, 21 cases (39.6 %) harbored an p53 mutation and 19 cases (35.8 %) harbored an ATRX. In addition, 1p19q co-deletion mutation was found in 7 cases (12.2%). We found that IDH1 and IDH2 are mutually entirely in gliomas. There was no significant relation between histopathology, tumor location and clinical finding with diagnosed mutations.
Conclusion: Our study discloses an associated distinction between IDH1 and IDH2 mutant gliomas nearly in half of patients, followed by p53. These mutations should be reviewed separately because their differences could have indication for the diagnosis and treatment of IDH1/2 mutant gliomas.

Keywords: Glioma; Mutation; Brain Tumor

Introduction

Based on the 2007 World Health Organization (WHO) categorization, glioma as the most common primary brain tumor, is classified as grade I to IV based on histopathological and clinical criteria WHO grade I gliomas are often treated by surgical evacuation, whereas WHO grade II or III gliomas are wildly invaded on brain and have a catastrophic prognosis [1,2]. WHO grade IV tumors (glioblastomas), demonstrated a mean survival rate of only 15-18 months, even after total resection considering of surgery and adjuvant therapy [3]. In past decade, the genes encoding IDH1 were depicted to be highly mutated in low-grade gliomas and a subgroup of GBM [4]. In further, IDH1 mutations were reported to find in 70–80 % of WHO grade II or III astrocytoma, oligodendrogliomas, and oligoastrocytomas, whereas a small group (3–5%) were found to harbor IDH2 mutations [5]. Moreover, mutations of IDH1,2 are mutually specific in gliomas, containing IDH1 mutations in 70–80% of cases [6,7]. In other type of brain tumors, diffuse astrocytoma frequently

carry TP53 mutations [8]. Oligoastrocytomas demonstrate either TP53 mutations or loss of 1p/19q [9]. Although the mutation that leads to 1p/19q codeletion is distinctive of oligodendroglioma, positive 1p/19q codeletion have been evaluated in cases with glioblastoma histopathology [10]. By itself, the 1p/19q codeletion, is inadequate for a diagnosis of gliomas and IDH-mutant or 1p/19q codeleted [11,12]. Due to lack of characterizing, a positive 1p/19q codeletion outcomes can be bewilder, especially in tumors without classic oligodendroglioma morphology [13,14]. The present research evaluates a quantitative basis for the genetical classification of gliomas by combining a number of patients from central institution. The specific purposes will determine the various combinations of genetic mutation and to assess whether molecular classification using IDH1 mutations, TP53 mutations, ATRX and 1p19qloss assess reliable outcome data.

Methods and Materials

Tumor Samples and Histology Review

Fifty- three samples of diffuse glioma of WHO from adults (patients' age, ≥20 years) from patients were obtained from 2016-2019 in Mashhad University of Medical Sciences. This study was performed after the approval of the Mashhad University of Medical Sciences Ethical Committee. (IR.MUMS.MEDICAL.REC.1400.487) Exclusion criteria were secondary tumor, history of chemotherapy, <20 years old and brain stem tumor. Histological sample review was carried out by two neuropathologists according to the WHO Classification of Tumors of the Central Nervous System. Whereby, after the pathology review, a total of 53 tumors were confirmed as diffuse gliomas. DNA was extracted from paraffin-embedded sections, as described previously. DNA quality was sufficient for genetic analyses for 53 cases. Clinical data including age and sex, location of tumors, histological diagnosis, date of surgical resection, extent of surgery, other treatment (radiotherapy, chemotherapy), date of last follow-up or last contact, and date of death were achieved.

Mutations of The IDH1 and IDH2 Genes

Single-strand conformational polymorphism analysis was taken to depicted for mutations in exon 4 of the IDH1 gene. Then, investigation for mutation of exon 4 of the IDH2 gene were evaluated in samples that gave negative results.

Tp53 Mutations

Screening for mutations in exons 5–8 of the TP53 gene were conducted single-strand configuration polymorphism analysis. Negative results sample were then investigated for mutations in exons 4, 9, and 10 using the following primers: 5′-CTGGTC CTCTGACTGCTCTTT-3′ (sense) and 5′-TGGCATTCTGGGAGCTTCAT-3′ (antisense),5′-GTCCAGATGAAGCTCCCAGA-3′ (sense) and TTCTGGGAAGGGACAGAAGA-3′ (antisense), 5′-TCTTCTGTCCCTTCCCAGAA-3′ (sense) and 5′-AACTGACCGTGCAAGTCACA-3′ (antisense) for exon 4; 5′-CCTTTCCTTGCCTCTTTCCT-3′ (sense) and 5′-CCACTTGATAAGAGGTCCCAAG-3′ (antisense) for exon 9; and 5′-TCCTCTGTTGCTGCAGATCC-3′ (sense) and 5′-AAGGGGCTGAGGTCACTCAC-3′ (antisense) for exon 10.

Loss of 1p/19q

Loss of 1p/19q was assessed using three microsatellite markers (D1S214, D1S468, and D1S2736) on chromosome 1p, and three markers (D19S408, D19S596, and D19S867) on chromosome 19q as described previously.

Statistical Analyses

The t-test was performed for comparison of the mean age of the patients. The Kaplan-Meier method and the log-rank test were confirmed for survival analysis. Cox regression models were assessed the effect of different combination of genetic alterations on the survival of patients after adjusting with patients' age, sex, and treatment (surgery and/or radiotherapy).

Results

In this study, the patients included in this study consist of 53 patients, 34 men (64.1%) and 19 women (3.9%) and mean age: 43.2 ± 10.08 years. T-test was done and there was no significant relation between age and sex.

Genetic Description

Because the mean age and survival of patients with IDH1 and those with IDH2 mutations were similar (P = 0.2520 and P = 0.6904, respectively), we combined IDH1 and IDH2 mutations for further analyses of combinations of genetic alterations, age distribution, and survival. In genetical study, most common histopathology was astrocytoma in 67.9% (36 patients), 14 patients in oligodendroglioma (26.4%) and mixed oligoastrocytoma in 3 patients (5.7%). Based on WHO criteria, 29 patients (54.7%) were grade 2, 16 patients (30.2%) were grade 1 and only 8 patients (15.1%) grade 3. We found that 24 cases (45.2%) of tumors were in frontal lobe, 11 cases (20.7%) in temporal, 10 cases (18.8%) in parietal, 6 cases (11.3%) in occipital and only two of them (3.7%) in insular lobe. Chi-square analysis showed no relation between tumors location and genetical mutations. (p=0.653).

Tp53 Mutations

One hundred forty-eight miscoding TP53 mutations were detected in 21 (39.6%) of all diffuse gliomas analyzed, and in 16 patients (44.4%) of diffuse astrocytoma, 4 patients (28.%) of oligodendrogliomas and 1 patient (33.3%) of oligoastrocytomas. There was no significant difference in distribution and type of TP53 mutations between different histological types. Base on WHO grading, TP53 was found in 14 patients (48.3%) of grade 2, 4 patients (32.9%) in grade 1 and 3 patients (18.8%) in grade 1 with no significant relation. (p=0.060).

IDH1 and IDH2 Mutations

IDH1,2 mutations were observed in 29 cases (54.7%) of all diffuse gliomas analyzed. IDH1 mutations were similarly frequent in all diffuse astrocytoma (61.1%), oligodendrogliomas (35.7%), and oligoastrocytomas (3.2%). Chi-square analysis showed no relation between tumors variants and genetical mutations. (p=0.653) Base on WHO grading, TP53 was found in 18 patients (62.1%) of grade 2, 5 patients (31.3%) in grade 1 and 6 patients (75%) in grade 1with no significant relation. (p=0.063).

Atrx Mutations

ATRX mutations were observed in 19 cases (35.8%) of all diffuse gliomas analyzed. Whereas, variable form was found in 8 patients (15.1%). ATRX mutations were similarly frequent in all diffuse astrocytoma (61.1 %), oligodendrogliomas (66.7%), and oligoastrocytomas (35.7%). Chi-square analysis showed no relation between tumors variants and genetical mutations. (p=0.603) Base on WHO grading, ATRX was found in 8 patients (50%) of grade 1, 8 patients (27.6%) in grade 2 and 3 patients (37.5%) in grade 1 with no significant relation. (p=0.490).

Loss of 1p/19q

Loss of 1p/19q was observed in 7 patients (13.2%) of all low-grade diffuse gliomas analyzed, and in 1 patient (2.8%) of diffuse astrocytomas, 6 patients (42.9%) of oligoastrocytomas. analysis showed significant relation between tumors variants and genetical mutations. (p=0.001) Base on WHO grading, Loss of 1p/19q was found in 2 patients (12.5%) of grade 1, 4 patients (13.8%) in grade 2 and 1 patients (12.5%) in grade 1 with no significant relation. (p=0.490) Overall, 6 months mortality rate was found in 18 patients (33.9%). As analysis showed, there were no significant relation between IDH1,2, P53, ATRX, 1p19q co-deletion and 6-months mortality rate. (p=0.26, p=0.502, p=0.356, p=0.12).

Discussion

Malignant diffuse glioma remains an outstanding threat to human health worldwide and impact a huge burden of diseases for health care systems. It is well established that the prognosis of patients with high-grade malignant glioma is considerably poor and IDH1/2 mutations have been detected in numerous of GBM patients [9]. We demonstrated the majority of low-grade diffuse gliomas carry at least one of the subheading genetic alterations: IDH1 mutation, IDH2 mutation, TP53 mutation, and 1p/19q loss. Most common histopathology was astrocytoma and grade 2 WHO.

These findings confirm previous data depicted that IDH1 mutations occur at a very early stage and are the most common genetic changes in astrocytic and oligodendroglia low-grade diffuse gliomas. Negative results in four genetical descriptive, suggests the alternative genetic roots involving as yet not identified genomes that lead pathogenesis of a small group of low-grade diffuse gliomas. The superiority of tumors with TP53 mutation and IDH1/2 mutation were histopathological diagnosed as diffuse astrocytoma, whereby only one-third of tumors with 1p/19q loss ± IDH1/2 mutation were oligodendroglioma. This demonstrate that tumor cells with IDH1/2 mutations disposed to have an astrocytic type. In oligodendroglioma, 1p19q co-deletion significantly showed higher among other tumors.

It is known that IDH1 mutations are a significant factor of approving outcome in patients with glioblastoma. Ramin et al, IDH mutation in more than 60 years old patients found that in 19.2% of astrocytoma and 50% of oligodendroglioma tumors [15]. Related tumors to IDH1/2-mutant are found to basically demonstrate in adolescents rather than younger children or adult [10,12]. We found that more than half of patients had IDH1, 2 mutation. There is growing engrosment in the prevalence of IDH1/2 mutations in various types of glioma. Whereas, Wang et al, demonstrated that IDH1,2 in 55.2% of patients with diffuse gliomas [1]. Kim et al showed 37% of patients with diffuse glioma had correlated IDH1,2 and 1p19q co-deletion mutations [16]. As we depicted, P53 mutation was found in 40% of diffuse glioma. So far, Jin et el. in meta-analysis study showed p53 in 41% of patient in low grade glioma and 63% in high grade one [17]. TP53 mutations and loss of 1p/19q is considerably important, since these changes are markers of poor and more approving outcomes, respectively.

Cancer Genome Atlas described 93% altered p53 mutation in patients with positive IDH mutation in diffuse glioma [18]. The prognostic role of IDH1 mutation in WHO grade II glioma remains unclear. One study in 49 patients with diffuse astrocytoma showed a significant relation

between the presence of IDH1 mutations and longer survival [19]. Despite IDH1/2 mutations are not prognostic, we proposed that IDH1/2 mutation be assessed, cause this is the most reliable factors for a diffuse WHO grade II glioma and excludes other gliomas, including pilocytic astrocytomas, ependymomas, and non-neoplastic [20,21]. As we showed, 35% of patients had ATRX mutations. Johnson et al. found that p53 mutation in 5.3% and ATRX in 24.2% of children in low grade glioma [22]. In addition, Brat et al. evaluated that BRAF, SMARCA4, ATRX and TP53 related to recurrency of diffuse gliomas [18].

Conclusion

In conclusion, our study discloses relation between IDH1, 2 mutant gliomas nearly in half of patients, following by p53. We provide further information that there were no association between histopathology, tumor location, clinical outcomes and IDH1, 2, ATRX, TP53 and 1p/19q codeletion. Further studies on the genetically results IDH mutation should lead to more comprehensive understanding of the underlying association between IDH mutations and their impacts on the outcome of diffuse gliomas.

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